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EXPOSURE TO AIR POLLUTION IN THE WORK AND RESIDENTIAL ENVIRONMENT DURING PREGNANCY AND ADVERSE BIRTH EFFECTS

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EXPOSURE TO AIR POLLUTION IN THE WORK AND RESIDENTIAL ENVIRONMENT DURING PREGNANCY AND ADVERSE BIRTH EFFECTS

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To my dear wife Anna, for all of your support always, you are my queen, and my kids, Frida and Ester, you are the biggest gifts in my life!

ABSTRACT

Air pollution is an environmental health risk that causes millions of premature deaths every year around the world. Air pollution exposure has been associated with respiratory and cardiovascular morbidity and an increased risk of lung cancer, and has also been associated with adverse birth effects. There is still some uncertainty about which compounds in air pollution that causes adverse birth effects. Few studies have assessed the association of occupational exposure to air pollutants and birth outcomes even though levels can be substantially higher in occupational settings than in ambient air in the residential area. No previous studies have assessed the joint effects of air pollution in residential and occupational settings in relation to adverse birth effects.

The overall aim of the study was to assess the relationship between the mothers' exposures to air pollution in the residential and occupational environment during pregnancy and negative health effects in their children, looking specifically at birthweight, small for gestational age and preterm birth.

The first two papers consisted of mother-child pairs from single births (995,843 observations) during 1994 to the end of 2012 and the occupational exposure to particles were assessed with a job exposure matrix. In the last paper we restricted the sample further, to include all single births from the beginning of 2007 to the end of 2012 (546,618 observations), and used a modelling system called SIMAIR to assess the exposure to air pollution in residential settings. All of the data in these nationwide cohorts came from Swedish national registers, which included important potential confounders and outcome variables.

The results show that working mothers with low absence and high exposure to organic and inorganic particles had an increased risk of adverse birth effects in form of preterm birth, low birthweight and small for gestational age.

The statistically significant odds ratio for high organic particle exposure: low birthweight (OR = 1.19; 95% CI: 1.07–1.32), small for gestational age (OR = 1.22; 95% CI: 1.07–1.38) or preterm birth (OR = 1.17; 95% CI: 1.08–1.27) compared to unexposed.

The statistically significant odds ratio for high inorganic particle exposure: preterm birth (OR = 1.18; 95% CI: 1.07–1.30), low birth weight (OR = 1.32; 95% CI: 1.18–1.48), and small for gestational age (OR = 1.20; 95% CI: 1.04–1.39) compared to unexposed.

Subgroup analyses showed that the increased risks associated with exposure to inorganic particles were driven by exposure to iron particles. Subgroup analyses of the compounds in organic particle exposure showed an increased risk of small for gestational age associated with oil mist exposure. Exposure to oil mist and cooking fumes was also associated with low birthweight, and other organic dust and paper was associated with preterm birth. No increased

risks were found in relation to exposure to stone and concrete particles.

An increased risk of small for gestational age (OR = 1.40; 95% CI: 1.15–1.71) was associated with exposure to combustion products. Welding fumes were also analysed separately and high exposure was associated with an increased risk of low birthweight (OR = 1.22; 95% CI: 1.02–1.45) and preterm birth (OR = 1.24; 95% CI: 1.07–1.42).

Residential exposure to combustion related particles (PM1) during the pregnancy was associated with a reduction in birthweight: Low exposure -15.3 g (95%CI: -19.4 g; -11.1 g), Moderate exposure -24.1g (95%CI: -28.4g;-19.8g), High exposure -29.0g (95%CI: -33.6g;-24.5g) compared to those in the very low exposed group.

No clear interaction effect on fetal growth was found after exposure to both occupational and residential particles during pregnancy, but an additive effect was suggested. Weak associations were found between residential exposure to particles and low birthweight or small for gestational age, while no increased risk was shown for preterm birth. Only a marginal effect was seen when using occupational exposure as a confounder in the analyses on residential air pollution.

Occupational exposure to organic (e.g. oil mist, paper dust, cooking fumes and other organic particles) and inorganic particles (e.g. iron particles), as well as combustion products (PAH) and welding fumes, have shown to be associated with an increased risk of adverse birth outcomes. The results strengthen the view that women should not be exposed to high levels of these particles during pregnancy, but the results needs to be confirmed in future studies.

Separate effects on birthweight were seen after exposure to particles in occupational and/or residential setting. The results implied that an overall exposure assessment of particles for each individual is needed when assessing risks, but further studies are needed to confirm these findings.

LIST OF SCIENTIFIC PAPERS

- I. Norlén F, Gustavsson P, Wiebert P, Rylander L, Albin M, Westgren M, et al. Occupational exposure to inorganic particles during pregnancy and birth outcomes: a nationwide cohort study in Sweden. *BMJ Open*. 2019;9(2):e023879.
- II. Norlén F, Gustavsson P, Wiebert P, Rylander L, Westgren M, Plato N, et al. Occupational exposure to organic particles and combustion products during pregnancy and birth outcome in a nationwide cohort study in Sweden. *Occupational and Environmental Medicine*. 2019;76(8):537.
- III. Norlén F, Gustavsson P, Wiebert P, Rylander L, Westgren M, Plato N, Albin M, Bennet C, Gidhagen L, Bellander T, Selander J. Residential air pollution during pregnancy and birth outcome in a nationwide cohort study in Sweden – is the association modified by occupational exposure to particles?
[Manuscript]

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LIST OF ABBREVIATIONS

SGA	Small for gestational age
LBW	Low birth weight (<2500g)
PTB	Preterm birth
JEM	Job-exposure matrix
FINJEM	Finnish job-exposure matrix
NYK	Nordic occupational classification
PAH	Polycyclic aromatic hydrocarbons
OR	Odds ratio
PM	Particulate matter

1 BACKGROUND

Air pollution is the contamination of the atmosphere by chemical, physical or biological agents and is one of the world's largest environmental health risks, responsible for about 3 million deaths from outdoor air pollution (WHO, 2014, WHO, 2016a).

Ambient air pollution (or smog) has been suspected to cause adverse health effects for a long time, but it was not really apparent until the London fog episode (1952), where the smog and the weather, with a ground level inversion and cold (condensation), led to a thick fog that lingered over London for several days and resulted in an dramatic increase of deaths in the weeks after (Royal Sanitary, 1954). Other significant steps towards understanding the associations between air pollution and people's health were the Six U.S. Cities study and the prospective study of adults on particulate air pollution as a predictor of mortality (ACS-study); both showed associations between mortality and long-term exposure to PM_{2.5} (Dockery et al., 1993, Pope et al., 1995). Air pollution exposure is now an established risk factor of lung cancer, respiratory and cardiovascular morbidity (WHO, 2013) and may also have an adverse effect on birth outcomes.

Associations between exposure to traffic-related air pollution at the residence during pregnancy (combustion products: SO₂, NO_x, CO and particles: PM_{2.5} and PM₁₀) and low birthweight, preterm birth and small for gestational age have been observed in different populations (Shah et al., 2011, Malmqvist et al., 2011, Chang et al., 2012, Leem et al., 2006, Olsson et al., 2012).

Few studies, however, have assessed the association between occupational particle exposure during pregnancy and birth outcomes, even though many occupationally active women are exposed. In addition, no previous study has assessed the combined effects of residential air pollution and occupational exposure to particles and adverse birth effects.

1.1 Exposure

Air pollution in residential and occupational settings are often studied separately and there are many times differences in both composition and measurements used. In residential settings, outdoor ambient air pollution in form of particulate matter usually consists of nitrates, ammonium, sulfates and other inorganic ions, elemental and organic carbon, crustal material, metals and particle-bound water, as well as polycyclic aromatic hydrocarbons (PAH), allergens and microbial compounds of varying mixture, depending on the geographic location (WHO, 2013).

Particulate matter (Jankovic et al., 2014) in the atmosphere is often categorised by its aerodynamic diameter, where a particle size of 0.1 micro metres or less is called the ultra-fine

fraction, a particle size of 2.5 micro metres or less is called the fine fraction and, a particle size between 2.5 to 10 micro metres is called the coarse fraction (Backes et al., 2013).

The ambient air pollution, in the form of particles, aggregate during transportation into the atmosphere (SLB-ANALYS, 2007). To monitor the particulate matter in outdoor air pollution it is usually quantified via PM_{10} or $PM_{2.5}$ metrics and sometimes PM_1 (Heal et al., 2012). When monitoring occupational exposure to particulate matter the categories often used are inhalable (PM_5) or respirable ($PM_{3.5}$), referring to the particle's depth of penetration into the lungs (Heal et al., 2012).

In occupational settings, the content of air pollution is slightly different from outdoor air pollution in the residential setting. The inorganic particles (e.g. plaster, concrete, iron and isolation material) and organic particles (e.g. paper, wood, oil and textile) mostly contain coarse particles, therefore they tend to deposit in the nasopharyngeal region (Chow, 1995), but there are also fractions within, which contain finer particles that may deposit further down in the alveolar and tracheobronchial regions of the lung.

Different combustion particles like diesel exhaust and some fractions of welding fumes (Willers et al., 2013, Swedish Work Environment Authority, 2013) usually contain finer particles. Particles from wood burning have different characteristics than combustion particles from diesel and petrol and have a tendency to be slightly larger (Hedberg et al., 2002).

Distribution of the particles in the respiratory system and where they deposit can be explained by particle size (see Fig.2.) but particle size does not explain the toxicity of different substances to the lung tissue (Hedberg et al., 2010, Morakinyo et al., 2016). There is a possibility that the distribution affects the causal pathways (see Fig.3.) and as such affects the outcomes differently, depending on the particulate matter size and constitution.

To assess occupational exposure, different methods are used. Personal sampling can give a high precision when assessing exposure, but it can be expensive and time-consuming. For an outdoor assessment of air pollution, some agents are monitored at certain places and they are then used to model other specific places or areas. In occupational settings, medicine sampling is sometimes used to make job exposure matrices which provide an assessment of exposures in different occupations. Those matrices can then be used for epidemiological studies.

1.1.1 Job-exposure matrices

According to Kauppinen et al. (1998), a job exposure matrix is basically a cross-tabulation of a list of job titles and a list of exposures and it is a tool that can be used to get information on exposure by using the information on job titles (see Fig.1.). Kauppinen et al. (1998) also conclude that a JEM saves resources and may, in large studies, be the only possible way to assess exposure. To use the matrix for epidemiological studies, the prevalence and intensity

needs to be connected to the occupation of the study subject, usually through a merge between the cohort and the JEM by occupational code.

NYK83		Asbestos		Lead		Iron	
Code	Occupation	P	C	P	C	P	C
750	Toolmakers, machine-tool setters and operators					90	0.077
751	Machinery fitters, machine assemblers	15	0.001	15	0.140	50	0.055
753	Sheet metal workers	30	0.007	15	0.070	60	0.137

Fig.1. Example of a job exposure matrix with occupational code, occupations in text, prevalence (%) and concentration for each agent.

1.1.2 Assessment of ambient air pollution

One of the methods used to estimate outdoor air pollution exposure is modelling. In the 2016 IMM report (Medicine, 2016), the authors state that an environmental factor, like air pollution, that shows different levels in different places, can be assessed with spatial analysis, but if the levels change with time, as they do for air pollution, a temporal analysis is important as well. The authors also wrote that if the sources and how they spread are known, and good geographical data is available, a source-receptor model (which combines spatial and temporal modeling) is possible.

The Swedish Meteorological and Hydrological Institutes (SMHI) national modelling system, SIMAIR (Gidhagen et al., 2009), is able to classify exposure levels on a specific address nationwide via calculations. For every address, concentrations of PM₁ and PM₁₀ can be calculated as daily mean levels (Gidhagen et al., 2009). The SIMAIR model for calculation has been used before in a nationwide study on outdoor air pollution and health effects in adults (Gidhagen et al., 2013).

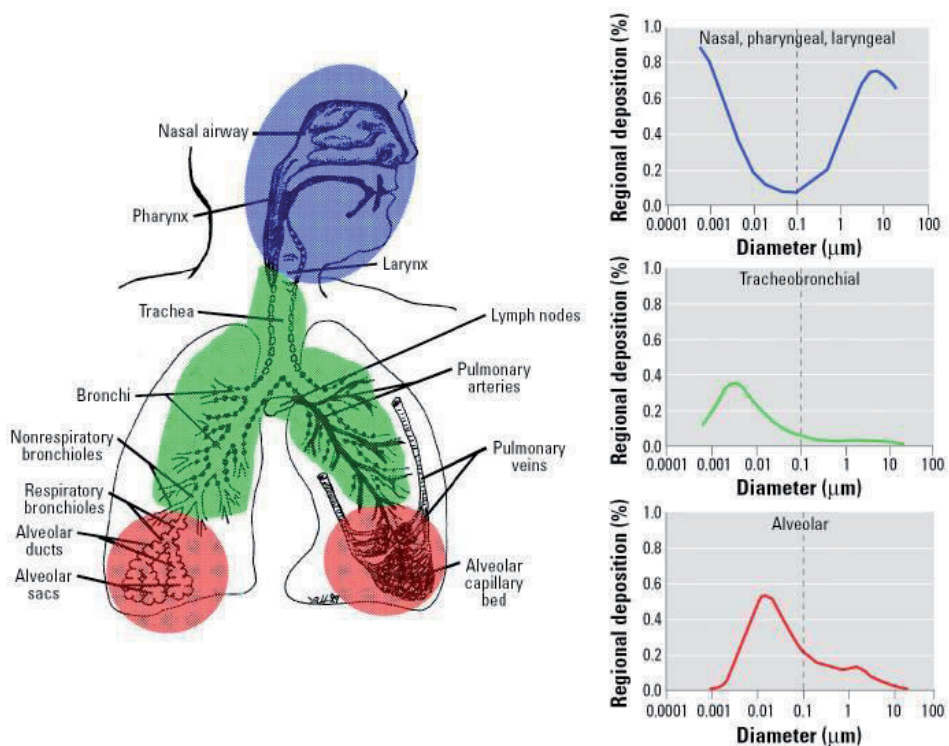


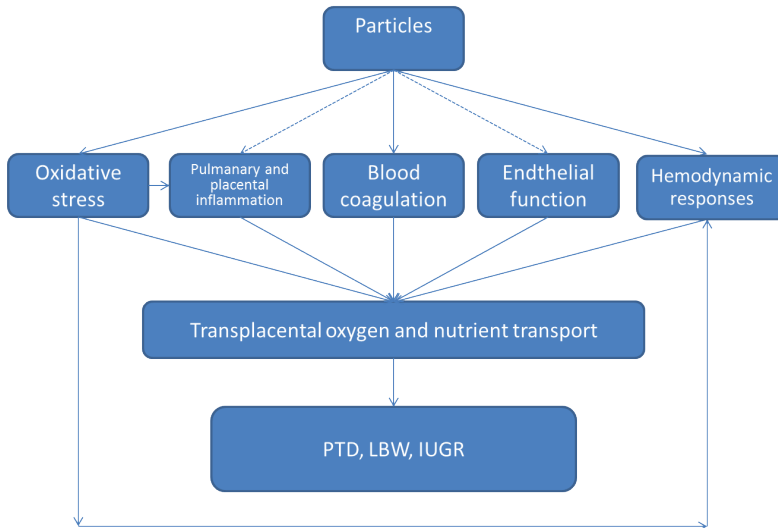
Fig.2. Fractional deposition of inhaled particles in the human respiratory tract. Source: Oberdörster et al. (2005). Reprinted with permission from Environmental Health Perspectives, © 2005. Figure based on data from the International Commission on Radiological Protection 1994. Drawing courtesy of Dr. Jack R. Harkema, Michigan State University.

1.2 Mechanism

The mechanism behind an association between exposure to air pollution during pregnancy and fetal health effects is not yet fully understood (Leem et al., 2006). Exposure to air pollution during pregnancy could lead to the inflammation and oxidative stress that has been associated with preterm birth, poor growth and low birthweight (Kannan et al., 2006, Ghosh et al., 2007, Perera et al., 1999). Inflammation and oxidative stress could also lead to gestational hypertension which is a risk factor for preterm birth (Leem et al., 2006). Oxidative stress can interfere with intrauterine growth due to vascular dysfunction in the placenta (Myatt et al., 2000).

Low birthweight (LBW) consists of two underlying causes, preterm delivery (PTD) and intrauterine growth retardation (IUGR), that partially cover each other and could plausibly be caused by cardiovascular mechanisms of inflammation, oxidative stress, endothelial function, hemodynamic responses and coagulation, see Fig.3 (Kannan et al., 2006).

Fig.3. Plausible causal pathways based on figure in Kannan 2006.



1.3 Outcome

Low birthweight (LBW) is usually defined as a birthweight less than 2500g (Hughes et al., 2017). Small for gestational age is used to describe when the baby's birthweight is below a certain centile for its gestation and indicates risk of fetal growth restriction (Elsevier, 2014). The outcome is estimated by a calculated growth curve of weight and gestational age. It is common to use 40 weeks or 280 days from the first day of the last menstrual period to estimate the date of birth for a full term pregnancy. Preterm birth is defined by a gestation of less than 37 completed weeks (Elsevier, 2014).

Adverse birth effects like low birthweight, small for gestational age and preterm birth, are relatively common conditions among newborns. About 3.7% to 5.1% of the children were born with a low birthweight and about 2.7% to 4.4% were born small for gestational age of the children effected between 1998 and 2007 in Sweden (National Board of Health and Welfare, 2009). Premature births accounted for about 5% of all single births (2013), and have done so in recent decades (National Board of Health and Welfare, 2014).

Low birthweight is associated with an increased risk of asthma and respiratory problems (Ali and Greenough, 2012) as well as cardiovascular disease (de Jong et al., 2012) and adverse effects on mental development later in life (Breslau et al., 1994). In addition, children with low birthweight have a higher mortality than children with normal birthweight (Kochanek et

al., 2012). Furthermore, preterm birth may result in cognitive deficits later in life (Nepomnyaschy et al., 2012, Cheong and Doyle, 2012). This means that any risk factor which can be identified and either eliminated or reduced, can be of great importance.

1.4 Previous research

Lamichhane et al. (2015) did a meta-analysis of exposure to particle matter (PM₁₀ and PM_{2.5}) in relation to adverse birth outcomes in the form of low birthweight and preterm birth. A total of 44 articles, mostly cohort studies, and 4 case control studies, meet the inclusion criterion. The study showed that birthweight was negatively associated with PM₁₀ and PM_{2.5} and that there was a significantly increased risk of PTB per 10 microgram increase in PM₁₀ and PM_{2.5} exposure, during pregnancy (Lamichhane et al., 2015). However, the authors point out that the results of previous studies are not consistent and it needs to be investigated further.

Another more recent systematic review and meta-analysis by Li et al. (2017) reached a similar conclusion when comparing the association between fine particulate matter (PM_{2.5}) and adverse birth outcomes in the form of low birthweight and preterm birth in 23 studies. The study found a significantly increased risk of preterm birth and an increased risk of low birthweight for an interquartile range increase in PM_{2.5} exposure during the pregnancy. The study identified a need for more prospective cohort studies and more precise exposure measurements to better characterise the associations between ambient fine particulate exposure and adverse birth outcomes (Li et al., 2017).

Regarding occupational exposure to particle matter during pregnancy and adverse birth outcomes, not many studies have been made. Quansah et al. (2009) have studied maternal exposure to welding fumes and metal dust and adverse pregnancy outcomes. The study population included 1,670 women from the Finnish Prenatal Environment and Health Study, in which 68 women were exposed to welding fumes or metal dust. The study concluded that there was some evidence of a higher risk of adverse birth outcomes if the mothers had been exposed to welding fumes, iron dust, or a combination during pregnancy (Quansah and Jaakkola, 2009). However, the study lacked exposure level data and recommend more studies be done to verify the results (Quansah and Jaakkola, 2009).

There has also been an epidemiological study conducted in Sweden (Li et al. 2010), using 816,310 singleton births from 1990 to 2004 from the Medical Birth Register. The study investigated the association between the parent's occupation (including 53 Nordic Occupational Classification groups) and the risk of adverse birth outcomes in the form of small for gestational age. The study showed that several of the mothers occupations (including mechanics and metal/iron ware workers and loaders, packers and warehouse workers) had a significant risk of adverse birth outcomes in the form of small for gestational age and requested that further research is completed in order to investigate which particle exposures in those occupations are connected with the risk of small for gestational age (Li et al., 2010).

Only two studies were found, one from China and one from Korea, that have assessed residential air pollution exposure stratified on occupational information and adverse birth outcomes. The information on occupation was crude, in the Chinese study on residential air pollution (PM_{2.5}) and preterm birth, the occupations were dichotomised into farmers and others (Guo et al., 2018). In the other study from Korea (Choe et al., 2019), the association between ambient air pollution (PM₁₀ and PM_{2.5}) and adverse fetal effects (SGA, LBW) was stratified into the employed and the unemployed. The Chinese study showed a slight increased risk of adverse birth outcomes for farmers in relation to others and the Korean study showed no effect modification between the employed and the unemployed.

1.5 Regulations

There are national regulations governing occupational activities where air pollution might occur. Air pollution can, in this case, refer to gases as well as particles. In the regulation 'Hygieniska gränsvärden' (AFS 2018:1), there are threshold values for about five hundred different substances (Swedish Work Environment Authority, 2015). These target the entire workforce, not just pregnant women. However, due to the particular risk in the work environment for pregnant women, there is another regulation called 'föreskrifterna om gravida och ammande arbetstagare' (AFS 2007:5). This regulation applies when the employer is informed that the woman is pregnant.

When there are known or suspected risk factors, according to 'föreskrifterna om gravida och ammande arbetstagare' (AFS 2007:5) at a workplace, an individual risk assessment of the working environment will be conducted. The employer is responsible for the risk assessment as a part of the systematic management of the work environment, according to the regulation 'Systematiskt arbetsmiljöarbete' (AFS 2001:1).

The Swedish Work Environment Authority has identified factors that might have negative health effects for pregnant or breastfeeding workers. These include noise, temperature and climate, working position and physical strain, biological substances, diseases, psychological strain, stress and violence, radiation, chemicals and underground work (Swedish Work Environment Authority, 2017). A few exposures, such as lead, are forbidden to work in during pregnancy or whilst breastfeeding (AFS 2007:5). In addition to the above regulations, there are additional regulations that bring up risks during pregnancy and breastfeeding, such as Berg och gruvarbete (AFS 2010:1), Dykeriarbete (AFS 2010:16), Mikrobiologiska arbetsmiljörisiker - smitta, toxinpåverkan, överkänslighet (AFS 2005:1), Rök och kemdykning (AFS 2007:7)(Swedish Work Environment Authority, 2017).

Sweden strives towards an overall environmental goal called 'Fresh air' and agents of concern are monitored and evaluated (Kyrklund, 2017). Sweden also has regulations for air quality in order to protect the environment and people's health, and to reach the environmental goal 'Fresh air' which also meets the criteria from the European Union (Swedish Environmental Protection Agency, 2014). The regulations start in the Environmental Code, Chapter 5, and are further specified in 'förordning med

miljökvalitetsnormer (MKN) för utomhusluft, luftkvalitetsförordningen' (2010:477) and 'Naturvårdsverkets föreskrifter om kontroll av luftkvalitet' (NFS 2016:9) (Swedish Environmental Protection Agency, 2014). There are air quality regulations for nitrogen dioxide/NO_x, particles (PM₁₀/PM_{2.5}), benzene, ground level ozone, carbon monoxide, nickel, cadmium and benzo (a) pyrene (Kyrklund, 2016). The Swedish Environmental agency also has new guidelines on air quality from 2019. There are other regulations that target air pollution, mostly by regulating sources of air pollution, but also international conventions like the UN Air Convention (UNECE/CLRTAP) (Swedish Environmental Protection Agency, 2014). Recently WHO have started updating the guidelines for ambient air exposure - including particle matter- (WHO, 2016b), since new evidence of adverse health effects (pregnancy-related outcomes are amongst those) has emerged.

A large amount of women are exposed to particle matter in outdoor and occupational settings during pregnancy. Since there are still uncertainties about the adverse effects of air pollution on birth outcomes (WHO, 2016a)(2), especially regarding occupational exposure, the legislation has not yet been able to include the full risk of exposure during pregnancy in their risk assessments and limits of exposure. The overall aim of this study is to contribute further knowledge of the association between exposure to particle matter and adverse birth outcomes.

2 AIM

The overall aim of this study is to assess the relationship between mothers' exposures to air pollution in the workplace and residential environment during pregnancy and the negative health effects this has on their children.

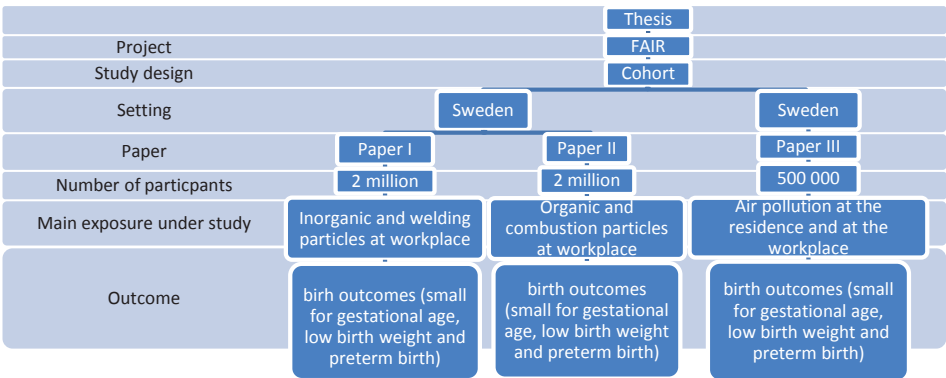
Specific Research Questions

- I. Does exposure to air pollution at work during pregnancy affect birth outcomes (preterm birth, low birthweight and small for gestational age)?
- II. Which type of air pollution in the work environment (organic dust, inorganic dust or combustion particles) is associated with negative effects on the fetus?
- III. Is the association between residential air pollution during pregnancy and negative health effects in children confounded by occupational exposure to air pollutants, and will a combination of residential and occupational exposure further increase the risk of negative birth outcomes?

3 MATERIAL AND METHOD

For an overview of the structure of the thesis, see Fig.4. below. The participants in Paper I and II consisted of all of the births from 1994 to the end of 2012. In Paper III, the participants consisted of a sample of about 500,000 mothers, for whom the residential air pollution exposure was calculated. The first paper explored the inorganic particles and welding fumes, and the second paper explored the organic particles and combustion particles with the outcome of adverse birth effects.

Fig.4.



3.1 Material and method

The FAIR study (Fetal Air Pollution Exposure) was based on registry data. Detailed information about the data sources, exposure assessment, outcomes and confounders are given below.

The study was based on linkages between the Medical Birth Register (MBR) at the National Board of Health and Welfare, the Population Register (RTB), the LISA-Register at Statistics Sweden, and the Register of Sick Leave and Parental Leave (MIDAS) from the Swedish Social Insurance Agency, see example in Fig.5.

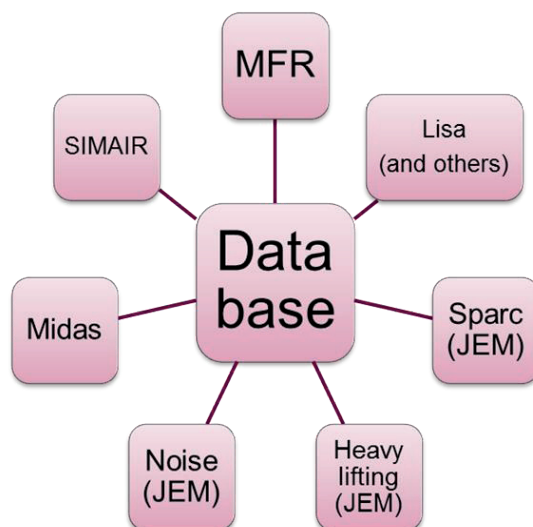


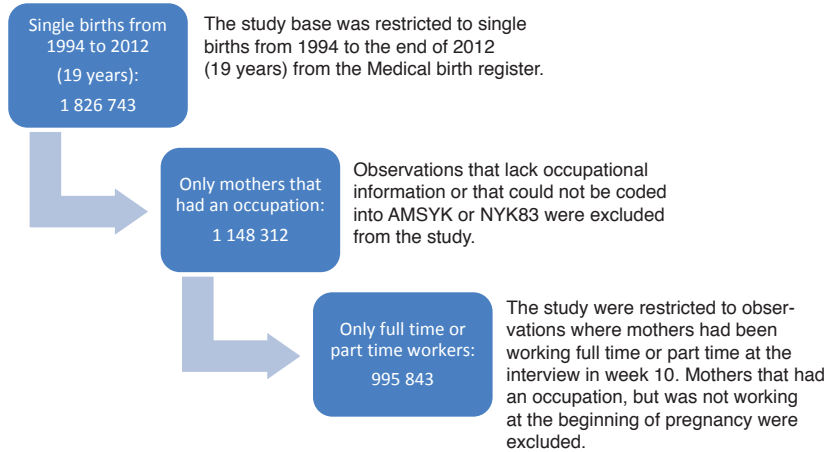
Fig.5. Example of the joint database.

The study population for Paper I and II comprised of all newborns in Sweden identified via the Swedish Medical Birth Register from the 1st of January 1994 to the 31st of December 2012. The data contains information about the mother's occupation in free-text (un-coded) and whether she was working full-time, part-time or not at all (at gestational week 10). It includes important information about the outcome variables such as the baby's characteristics (preterm birth, birthweight and small for gestational age), but also important information about potential confounders such as the mother's weight and height, multiple birth, parity, maternal smoking habits, nationality and family situation.

To increase the quality of data regarding occupational exposure, we have mapped absence from work with information collected from the Swedish Social Insurance Agency Register about sick leave and parental leave for every pregnancy between 1994 to the end of 2012. We then matched this with information from the Medical Birth Register with respect to gestational length and birth date, to assess the number of days of absence from work during pregnancy. To adjust for socioeconomic status, information about length of education has been collected from Statistics Sweden's (SCBs) LISA Register. Job exposure matrices on noise exposure, psychosocial stress at work and physical workload in occupational settings have been included as covariates in the analyses to adjust for potential confounding.

Only singleton births were selected ($n=1,826,743$). The women were included in the study if they had an occupation that could be coded into AMSYK (Standard Classification of Occupations from National Labour Market Board Sweden) or NYK 83 (Nordic Classification of Occupations from 1983), leaving 1,148,312 mother-child pairs in the sample. The study was further restricted to full-time or part-time workers, excluding those who stated an occupation but did not work in the beginning of pregnancy, leaving 995,843 observations in the study, see Fig.6.

Fig.6.



3.2 Confounders

A review of previous studies on pregnancy outcomes in the form of preterm birth, small for gestational age and low birthweight in association with exposure to occupational or residential air pollution was done to identify potential confounders (Triche and Hossain, 2007, Palmer et al., 2013, Baba et al., 2013, Windham and Fenster, 2008, Klepac et al., 2018).

Identified occupational confounders (more than 5% change in point estimate in the crude model) were: noise exposure, psychosocial stress at work and physical work load in occupational settings that may be correlated with occupational particle exposure, and potentially also with small for gestational age, low birthweight and preterm birth.

Other potential confounders found were the mother's characteristics: age, BMI, smoking, nationality, parity, socioeconomic factors such as their education level, family structure and the child's characteristics (gender and birth year). Previous studies show that the difference in birthweight between socioeconomic groups can be almost entirely explained by income, length of education and smoking (Ericson et al., 1993).

Regarding residential settings, the confounders were tested and restricted to more than a 3% change in point estimate in the crude model. Even if the change in point estimate was below 3%, the mother's age remained in the model.

Potential confounders that were chosen in the analysis of residential exposure and birth outcomes were current smoking habits (smokers (10 cigarettes per day or more), smokers (1-9 cigarettes per day) and non-smokers), nationality (Swedish, EU15/Nordic countries except Sweden, or outside EU15), socioeconomics of the surrounding area (+/-), the highest

completed education level (high school (2 years or less), university (less than 3 years), university (3 years or more or graduate)), exposure to ground level ozone (quartiles), the children's birth year, occupational exposure (+/-), parity (first child, second child or more), and the mother's age (three categories in intervals of five years).

The potential socioeconomic confounder variable was made dichotomous out of the 90th percentile of middle income per year (equal or higher than 285,024 SEK) and the 90th percentile of education level (above high school) within the surrounding area of the residence (Small Areas for Market Statistics). The socioeconomic variable was made to avoid a variable (like SES) based on occupation. The potential confounding exposure of ground level ozone has been previously used in a traffic pollution related study (Olsson et al., 2015, Olsson et al., 2012).

3.3 Occupational exposure assessment

Wiebert et al. (2012) developed a JEM for particulate matter which is presented in detail elsewhere (Wiebert et al., 2012). The matrix now includes estimations for fourteen different groups of particles for about 100 different occupational groups and 2 time periods. Exposure to particles is expressed as prevalence and intensity (concentration in mg per cubic metre) of exposure, see example in Fig.1.

The JEM contains groups of inorganic particles including iron dust, concrete dust and other inorganic dust. The subgroup of iron dust contains occupational airborne exposure to iron dust or fumes from welding, grinding, smelting or other processing of steel and other materials containing iron, including all iron compounds and metallic iron. The subgroup of other inorganic dust contains dust from plaster and insulation and the subgroup of concrete dust contains dust from stone and concrete material.

For organic particles there are 7 different subgroups: wood dust, dust from living animal, pulp or paper dust, dust from textiles, flour dust, exposure from metal processing or drilling oil, smoke from heated cooking fat, and other organic particles (e.g. dust from the earth, lead, plastic and soot).

The JEM also includes exposure to combustion particles such as diesel exhausts, welding fumes and PAH (Polycyclic Aromatic Hydrocarbons). Welding fumes are difficult to define because they contain many different compounds and both small and large particles (Swedish Work Environment Authority, 2013).

These different sources of particle exposure in an occupational setting have earlier been associated with negative health outcomes or have been suspected of causing negative health outcomes within the working force (Wiebert et al., 2012, Sjogren et al., 2013, Donham et al., 1989, Langlois et al., 2014).

The particle exposure in the work environment was aggregated into two major groups; inorganic particles (e.g. concrete dust) and organic particles (e.g. textile particles and flour dust). Particles generated by combustion (welding fumes, diesel exhaust in form of NO² and PAH) were analysed separately). Information on the mother's occupation (free text) was retrieved from the register interview in the Medical Birth Register and coded to the Swedish version of ISCO-88 (Selander et al., 2016).

The JEM was previously coded to the Swedish version of ISCO-58 and then converted to the Swedish version of ISCO-88 in order to connect with the Medical Birth Register. In this study a data file with the occupations in text and the corresponding Swedish version of ISCO-88 codes (6 figures) was merged with the occupations in text found in the Medical Birth Register. Then we merged a data file with the Swedish version of ISCO-58 and the corresponding Swedish version of ISCO-88 onto the JEM with the Swedish version of ISCO-58. That allowed us to connect the Medical Birth Register with the JEM using the Swedish version of ISCO-88. Afterwards, with help from occupational hygienists, we checked the exposed occupations and changed the exposure to zero if it was obviously misclassified.

In order to take presence at work into account, the analysis was stratified in to three categories: working full-time or part-time with high absence from work, working full-time or part-time with moderate absence from work and working full-time with low absence from work (see also appendix I and II). In the residential setting the mothers who were not working at all were included (with one exception) in the interaction analysis on occupational and residential exposure. The occupational exposure was restricted to mothers that had low absence from work and those who stated that they were not working were excluded. The analysis of exposure to organic/inorganic particles and welding fumes was divided in to high exposure, low exposure and no exposure. The subgroup analysis was dichotomized into unexposed and exposed.

3.4 Residential air pollution assessment

The mother's home address at the time of pregnancy was collected from Statistics Sweden's Population Register (RTB). All the addresses have been geocoded by Statistics Sweden and an exposure classification for each address has been made through calculations in the Swedish Meteorological and Hydrological Institutes (SMHI) National Modelling System, SIMAIR (Gidhagen et al., 2009). In this project, the SIMAIR model was used to calculate about 500,000 addresses where the pregnant mothers have lived during pregnancy between 2006 and 2012.

The sum of three sources on different scales, the regional (long-range transported air pollution from Europe and other Swedish regions), urban (impact from the city's different sources) and local (traffic sources within a radius of 250m) contribution was used to determine the mean level of air pollution on the mother's address during pregnancy.

The local contribution to ambient air pollution was calculated from exhaust derived and non-exhaust derived emissions. The exhaust derived emissions estimates from single roads was calculated using statistics on type and size of the roads, type of vehicle, fuel and driving pattern, and time variation of traffic. The non-exhaust emissions from traffic were calculated with a model (Omstedt et al., 2011) including estimates on humidity (metrological data) and dust (regional statistics based on assumptions of accumulated roadwear) on the road and the assumptions of swirl.

To calculate the urban contribution, an urban dispersion model (BUM) that uses a backward trajectory model for ground emissions (e.g. traffic) was used (Andersson et al., 2010, Andersson and Omstedt, 2013). The model calculated levels in a 1x1km square grid. For elevated point source emissions, a dispersion model was used (Omstedt, 1988), and to obtain metrological data, the MESAN system was used (Häggmark et al., 2000). The finite-length line source model, Dispersion ROAD (Omstedt et al., 2011), was also used to calculate the air pollution contribution in the immediate surroundings with a radius of 250m.

The regional contribution of ambient air (PM_{10} and $PM_{2.5}$) has a rather different composition of agents compared to local and urban sources, constituting to a large part of the secondary inorganic aerosols (including nitrate, ammonium and sulfate) and marine salts that are considered to be less harmful than fresh traffic related emissions, see Fig.7. The calculation of regional contribution (PM_{10}) by SIMAIR and the association to respiratory health showed no statically significant effects (Willers et al., 2013). Therefore, the analysis done with exhaust and non-exhaust derived residential air pollution from local and urban sources (PM_1 and PM_{1-10}) excluded regional background (PM_{10}).

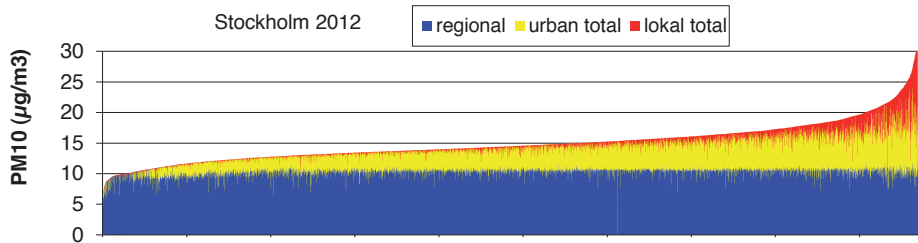


Fig.7. Observations (on the x-axel) of mean exposure during pregnancy in 2012 in Stockholm County. The exposure is divided into emissions closest to the address (local total), the closest city (urban total) and the rest of Sweden and Europe (regional).

3.5 Data analysis

The analyses of the occupational exposure and birth effects (low birthweight small for gestational age and preterm birth) have been done with multivariable logistic regression in STATA SE V.13.1 (StataCorp, College Station, Texas, USA) and the results reported as odds ratios (OR) with a 95% confidence interval (CI) and the analyses were adjusted for potential confounders.

We have also analysed which types (PM_1 and PM_{1-10}) of air pollutants in the residential environment during the pregnancy (calculated with the SIMAIR model) that were associated with fetal effects (small for gestational age, preterm birth and low birthweight). Analyses on residential exposure to particles were reported as odds ratio (OR) with a 95% confidence interval (CI) regarding small for gestational age, preterm birth and low birthweight and beta coefficients with a 95% confidence interval (CI) for birthweight (g). The analyses were done with both multivariable logistics, for low birthweight, preterm birth and small for gestational age, and linear, for birth weight regression. The analyses were also adjusted for potential confounders.

3.6 Ethical consideration

The study was registry based and involved human participants, but for this type of study it is not required to have formal consent. The procedures performed were in line with the 1964 Helsinki Declaration and its later amendments, the ethical standards of the national research committee and institutional and/or comparable ethical standards. The research group has not handled personal identification numbers or contacted any study participants. The analyses were presented in such a way that no individuals could be identified. Ethical permission was granted by the Regional Ethical Review Board in Stockholm on 8/14/2014 (case number: 2014/1108-31/5) and 6/28/2019 (case number: 2019-03606). The code key was stored at Statistics Sweden. To meet new regulations on data storage, the database was transferred to Secure-Lan in 2017.

4 RESULTS

4.1 Occupational exposure

The final study population constitute of 995,843 observations. The studies of organic and inorganic exposure included 46,044 cases of preterm birth, 28,272 cases of low birthweight and 20,445 cases of small for gestational age.

Baseline characteristics for the study population showed that the risk for adverse birth effects varied with the mother's age and seemed to be higher for older and younger mothers. Non-smokers had lower percentage of adverse outcomes than smokers. Lower prevalence of adverse birth outcomes was correlated with higher education. Mothers born outside Europe had a higher prevalence of cases than mothers with other nationalities.

The occupational exposure was grouped into organic and inorganic particles, except for welding fumes, PAH and diesel exhaust (NO₂) which was analysed separately. High exposure to inorganic particles during pregnancy vs no exposure was associated with babies born small for gestational age (adjusted odds ratio [AOR] = 1.20; 95% confidence interval [CI]: 1.04- 1.39), as well as with low birthweight (adjusted OR = 1.32; 95% CI: 1.18- 1.48) and pre-term births (adjusted OR = 1.18; 95% CI: 1.07- 1.30), among full-time working mothers with less than 50 days (median) leave of absence during pregnancy, see Tabel1. The effect was linked to a greater level of exposure to iron particles (including welding) than to concrete dust or other inorganic dust. See results tables for more information.

Table 1. Maternal occupational exposure^d to inorganic particles and small for gestational age (SGA)^a, low birthweight (LBW)^b, and preterm birth (PTB)^c subdivided by work participation during pregnancy.

	Working full-time with low absence from work ^e				Working full or part-time with moderate absence from work ^f				Working full or part-time with high absence from work ^g			
	Crude		Adjusted ^h		Crude		Adjusted ^h		Crude		Adjusted ^h	
	(n=376,831)	No of cases	OR (95% CI)	(n=370,126)	(n=418,233)	No of cases	OR (95% CI)	(n=410,370)	(n=200,779)	No of cases	OR (95% CI)	(n=196,878)
SGA	No Exposure	1	8,736	1	8,551	1	8,010	1	7,828	1	2,927	1
	Low Exposure	.83 (.71–.97)	156	.88 (.75–1.03)	154	.75 (.58–.99)	54	.89 (.68–1.16)	54	.85 (.60–1.21)	32	1.02 (.72–1.46)
	High Exposure	1.35 (1.17–1.55)	207	1.20 (1.04–1.39)	203	1.21 (1.05–1.39)	210	1.06 (.92–1.22)	204	1.19 (.98–1.44)	113	.97 (.80–1.17)
LBW	No Exposure	1	13,085	1	12,838	1	9,975	1	9,742	1	4,119	1
	Low Exposure	.84 (.73–.95)	236	.90 (.79–1.03)	230	.98 (.79–1.21)	87	1.11 (.89–1.38)	85	.73 (.53–1.01)	39	.84 (.61–1.16)
	High Exposure	1.52 (1.36–1.70)	346	1.32 (1.18–1.48)	341	1.11 (.98–1.26)	240	1.02 (.90–1.17)	235	1.08 (.91–1.28)	145	.93 (.78–1.11)
PTB	No Exposure	1	21,003	1	20,630	1	15,904	1	15,551	1	7,469	1
	Low Exposure	.83 (.75–.92)	377	.89 (.80–.99)	366	.89 (.75–1.07)	127	.98 (.82–1.17)	125	.75 (.60–.95)	73	.82 (.65–1.04)
	High Exposure	1.38 (1.26–1.51)	502	1.18 (1.07–1.30)	491	.99 (.89–1.10)	342	.93 (.83–1.04)	334	1.01 (.89–1.16)	247	.93 (.81–1.06)

^a Small for gestational age, estimated by a calculated growth curve of weight and gestational age.

^b Low birth weight, dichotomised as <2,500 g and ≥2,500 g.

^c Preterm birth, dichotomised as <37 weeks and ≥37 weeks.

^d Exposure divided into unexposed (0), low exposure (>0–50th percentile), and high exposure (>50th percentile). The 50th percentile = 0.09 mg/m³.

^e Full-time workers who stated that they were working full-time at the interview in week 10 and had fewer than 50 days of absence from work (<50th percentile) during pregnancy (excluding the first 14 days of sickness).

^f Part-time workers who stated that they were working part-time at the interview in week 10 or had 50 or more days (≥50th percentile) but fewer than 112 days of absence from work (<75th percentile) during pregnancy (excluding the first 14 days of sickness).

^g All workers who responded to the question about work at the interview in week 10 and had 112 or more days of absence from work (≥75th percentile) during pregnancy, except those who stated that they were not working at all.

^h Odds Ratio (OR) adjusted for mother's age, education, smoking habits, nationality, occupational exposure to noise, and parity.

High exposure to organic particles in the working environment (organic dust or particles from combustion) was also associated with adverse fetal effects (small for gestational age, low birthweight and preterm birth). Working mothers with a low absence and high exposure to organic particles had an increased risk of adverse birth effects in the form of low birthweight (OR=1.19; 95% CI: 1.07 to 1.32), small for gestational age (OR= 1.22; 95% CI: 1.07 to 1.38) and preterm birth (OR=1.17; 95% CI 1.08 to 1.27), see Table 2.

Table 2. Maternal occupational exposure^d to organic particles and SGA^a, LBW^b, and PTB^c subdivided by work participation during pregnancy.

	Working full-time with low absence from work ^e				Working full or part-time with moderate absence from work ^f				Working full or part-time with high absence from work ^g			
	Crude		Adjusted ^h		Crude		Adjusted ^h		Crude		Adjusted ^h	
	OR (95% CI)	No of cases	OR (95% CI)	No of cases	OR (95% CI)	No of cases	OR (95% CI)	No of cases	OR (95% CI)	No of cases	OR (95% CI)	No of cases
SGA												
Unexposed	1	8,353	1	8,187	1	7,144	1	6,998	1	2,631	1	2,572
Exposed (y/n)	1.29 (1.20-1.40)	746	1.14 (1.04-1.25)	721	1.28 (1.20-1.37)	1,130	1.11 (1.02-1.20)	1,088	1.30 (1.18-1.44)	441	0.97 (0.85-1.11)	425
Low Exposure	1.19 (1.08-1.32)	430	1.10 (0.98-1.22)	422	1.19 (1.10-1.30)	573	1.08 (0.98-1.20)	560	1.15 (1.00-1.33)	201	0.93 (0.79-1.10)	195
High Exposure	1.46 (1.30-1.64)	316	1.22 (1.07-1.38)	299	1.39 (1.27-1.52)	557	1.14 (1.02-1.26)	528	1.46 (1.28-1.67)	240	1.01 (0.86-1.19)	230
<i>P for trend</i>			0.001				0.013				0.942	
LBW												
Unexposed	1	12,492	1	12,272	1	9,049	1	8,859	1	3,748	1	3,649
Exposed (y/n)	1.37 (1.29-1.46)	1,175	1.15 (1.07-1.23)	1,137	1.12 (1.05-1.19)	1,253	1.03 (0.95-1.11)	1,203	1.15 (1.05-1.26)	555	0.94 (0.84-1.05)	530
Low Exposure	1.29 (1.19-1.40)	692	1.12 (1.03-1.22)	675	1.05 (0.96-1.13)	638	0.99 (0.91-1.09)	616	1.06 (0.93-1.20)	263	0.92 (0.79-1.06)	253
High Exposure	1.50 (1.37-1.65)	483	1.19 (1.07-1.32)	462	1.21 (1.11-1.31)	615	1.07 (0.97-1.18)	587	1.25 (1.10-1.41)	292	0.96 (0.83-1.11)	277
<i>P for trend</i>			0.000				0.264				0.445	
PTB												
Unexposed	1	19,995	1	19,654	1	14,476	1	14,179	1	6,832	1	6,658
Exposed (y/n)	1.39 (1.32-1.46)	1,887	1.16 (1.10-1.23)	1,833	1.06 (1.01-1.11)	1,897	0.98 (0.92-1.05)	1,831	1.09 (1.01-1.16)	957	1.00 (0.91-1.09)	929
Low Exposure	1.34 (1.26-1.43)	1,142	1.15 (1.08-1.24)	1,118	0.98 (0.92-1.05)	960	0.93 (0.86-1.00)	932	1.01 (0.92-1.11)	458	0.95 (0.86-1.06)	450
High Exposure	1.46 (1.35-1.57)	745	1.17 (1.08-1.27)	715	1.15 (1.08-1.23)	937	1.05 (0.97-1.14)	899	1.17 (1.07-1.28)	499	1.04 (0.94-1.17)	479
<i>P for trend</i>			0.000				0.565				0.645	

a. Small for gestational age, estimated by a calculated growth curve of weight and gestational age.

b. Low birth weight, dichotomised as <2,500 g and ≥2,500 g.

c. Preterm birth, dichotomised as <37 weeks and ≥37 weeks.

d. Exposure divided into unexposed (0), low exposure (>0–50th percentile), and high exposure (>50th percentile). The 50th percentile = 0.08 mg/m³.

e. Full-time workers who stated that they were working full-time at the interview in week 10 and had fewer than 50 days of absence from work (<50th percentile) during pregnancy (excluding the first 14 days of sickness).

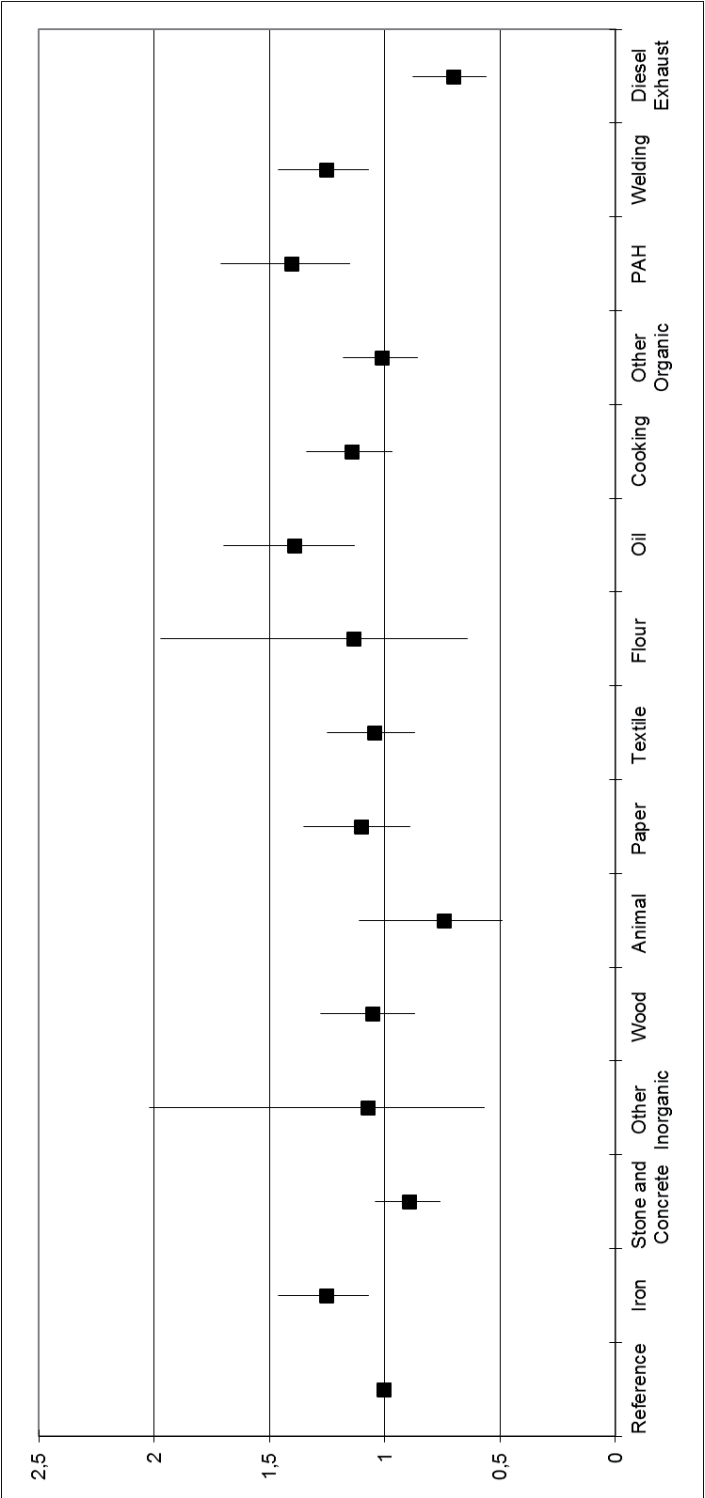
f. Part-time workers who stated that they were working part-time at the interview in week 10 or had 50 or more days (≥50th percentile) but fewer than 112 days of absence from work (<75th percentile) during pregnancy (excluding the first 14 days of sickness).

g. All workers who responded to the question about work at the interview in week 10 and had 112 or more days of absence from work (≥75th percentile) during pregnancy, except those who stated that they were not working at all.

h. Odds Ratio (OR) adjusted for mother's age, education, smoking habits, nationality, occupational exposure to noise, and parity.

Sub analysis of organic and inorganic particles in working mothers with low absence from work was made in order to identify which agents that increased the risk of small for gestational age, see Table 3 below. The adjusted odds ratio for all analyzed agents were: Iron (AOR=1.25; 95% CI: 1.07 to 1.46), Stone and Concrete (AOR=0.86; 95% CI: 0.76 to 1.04), Other Inorganic (AOR=1.07; 95% CI: 0.57 to 2.02), Wood (AOR=1.05; 95% CI: 0.87 to 1.28), Animal (AOR=0.74; 95% CI: 0.49 to 1.11), Paper (AOR=1.10; 95% CI: 0.89 to 1.35), Textile (AOR=1.04; 95% CI: 0.87 to 1.25), Flour (AOR=1.13; 95% CI: 0.64 to 1.13), Oil Mist (AOR=1.39; 95% CI: 1.13 to 1.70), Cooking Fumes (AOR=1.14; 95% CI: 0.97 to 1.34), Other Organic (AOR=1.01; 95% CI: 0.86 to 1.18). We also included agents in Table 3 that we have analysed separately: PAH (AOR=1.40; 95% CI: 1.15 to 1.71), Welding (AOR=1.25; 95% CI: 1.07 to 1.46) and Diesel (using NO₂ as a proxy) Engine Exhaust (AOR=0.70; 95% CI: 0.56 to 0.88). The agents that showed a statistically significant adjusted odds ratio for a low birthweight outcome were: Iron Particles, Welding Fumes, PAH, Oil Mist and Cooking Fumes, and for a preterm birth outcome it was: Welding Fumes, Paper Dust, Cooking Fumes and Other Organic particles (data not shown for low birthweight and preterm birth).

Table 3. Subanalysis of agents in Inorganic and Organic particles, as well as Welding Fumes, PAH and Diesel Engine Exhaust (NO₂) in association with the outcome of small for gestational age among mothers working full-time with a low absence from work.



4.2 Residential exposure

The air pollution outdoors at the home address in relation to birth outcomes (small for gestational age, low birthweight and preterm birth) and the joint effect between exposures in residential and occupational settings has also been investigated and analysed. In total, the analysis included 546,168 mother and child pairs. The analyses on residential exposure were adjusted for occupational exposure with only marginal effects.

Mothers exposed to higher levels of residential air pollution tend to have a higher educational level and to work full time during pregnancy compared to mother's with low exposure to residential air pollution. Exposed mothers also tend to be older and less likely to be smokers than mothers with low exposure. Exposure level differs slightly between birth years, with a higher amount of exposed mothers in later years. Nationalities also differ and there were fewer Swedish nationals among the exposed. Among mothers with low residential exposure to particles there were more prevalent with occupational exposure to particles. Parity differs between groups with fewer children in the exposed groups.

In Table 4, combustion related particles (PM₁) in the residential area during pregnancy was associated with a reduction in birthweight when comparing High exposed -29.0g (95%CI: -33.6g;-24.5g), Moderate exposed -24.1g (95%CI: -28.4g;-19.8g) and Low exposed -15.3 g (95%CI: -19.4 g;-11.1 g) to Very low exposed. A similar pattern was found for PM₁₋₁₀.

Table 4. Maternal residential exposure^a to particles during pregnancy in relation to birthweight in grams.

Table 4	PM ₁ from local and urban sources		PM ₁₋₁₀ from local and urban sources	
	Crude ^b	Adjusted ^c	Crude ^b	Adjusted ^c
	(n= 546,049) Reduction in birth weight in grams (g)	(n=536,367) Reduction in birth weight in grams (g)	(n= 546,049) Reduction in birth weight in grams (g)	(n=536,367) Reduction in birth weight in grams (g)
per µg/m ³	-16.3 (-17.8,-14.7)	-11.5 (-13.2,-9.8)	-9.7 (-10.6,-8.7)	-4.7 (-5.8,-3.7)
10 th to 90 th percentile	-37.7 (-41.2,-34.2)	-26.6 (-30.5,-22.6)	-27.7 (-30.5,-25.0)	-13.6 (-16.6,-10.6)
Very low exposed	1	1	1	1
Low exposed	-36.6 (-40.7,-32.5)	-15.3 (-19.4,-11.1)	-23.5 (-27.6,-19.4)	-12.7 (-16.8,-8.6)
Moderate exposed	-42.1 (-46.2,-38.0)	-24.1 (-28.4,-19.7)	-44.7 (-48.8,-40.6)	-24.6 (-28.9,-20.4)
High exposed	-49.2 (-53.3,-45.0)	-29.1 (-33.7,-24.5)	-55.0 (-59.1,-50.8)	-28.5 (-33.0,-23.9)

a. Exposure divided into unexposed, $\leq 0.01 \mu\text{g}/\text{m}^3$ (0-25th percentile), low exposure; $0.01 \mu\text{g}/\text{m}^3 >$, $\leq 0.72 \mu\text{g}/\text{m}^3$ (>25 -50th percentile), moderate exposure; $0.72 \mu\text{g}/\text{m}^3 >$, $\leq 1.57 \mu\text{g}/\text{m}^3$ (>50 th -75th percentile), and high exposure; $1.57 \mu\text{g}/\text{m}^3 >$ (>75 th percentile) for PM₁ and unexposed, $\leq 0.05 \mu\text{g}/\text{m}^3$ (0-25th percentile), low exposure; $0.05 \mu\text{g}/\text{m}^3 >$, $\leq 0.48 \mu\text{g}/\text{m}^3$ (>25 -50th percentile), moderate exposure; $0.48 \mu\text{g}/\text{m}^3 >$, $\leq 1.50 \mu\text{g}/\text{m}^3$ (>50 th -75th percentile, and high exposure; $1.50 \mu\text{g}/\text{m}^3 >$ (>75 th percentile) for PM₁₋₁₀

b. Restricted on smoking and occupation in text (not missing) tunnels and single births.

c. Adjusted for mother's age, smoking habits, occupational exposure, education, socioeconomic, exposure to ground level ozone, nationality, parity and birth year of the child.

The distribution of birthweight; a comparison between Single births where mothers were high exposed and very low exposed to PM_{10} with the low birthweight value marked is shown in Fig.8.

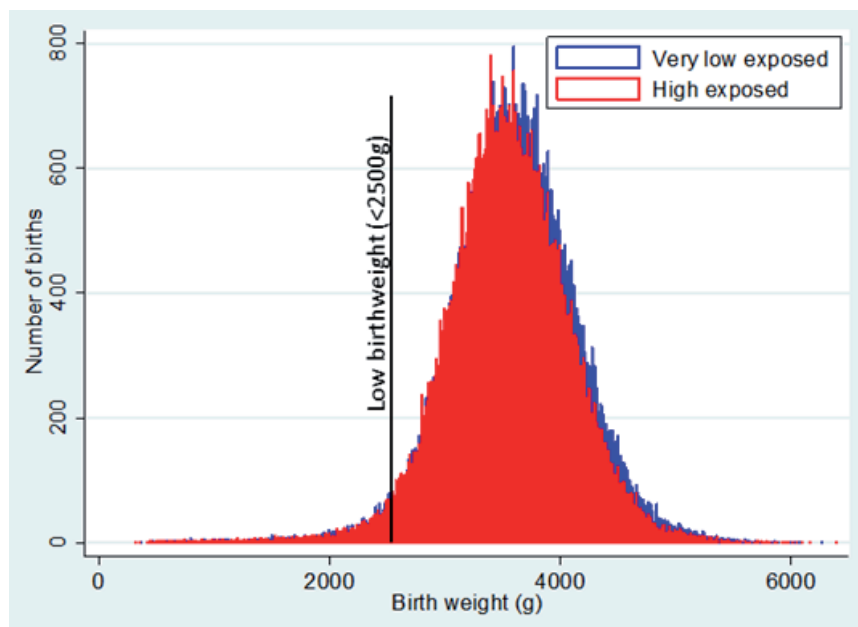


Figure 8 shows the difference in birthweight between single births with mothers exposed to very low level of PM_{10} and mothers exposed to high levels of PM_{10} . The figure also shows that among single births where the mother had high levels of residential exposure to PM_{10} the decrease of birthweight seems to be more associated with normal weight and heavier children than children with lower birthweight.

In Table 5 the results from the analysis of exhaust PM_{10} particle exposure in relation to birth outcomes showed an increased risk for small for gestational age. The adjusted odds ratio for High (1.07 (1.01-1.14)), Moderate (1.06 (1.00-1.12)), and Low (1.06 (1.01-1.12)) was compared to Very low exposure but no trend was found. The continuous exposure variable showed an adjusted odds ratio (AOR) of 1.02 (0.99-1.04) per $\mu g/m^3$ PM_{10} and the analysis of the difference in risk between the 10th and 90th percentile showed an adjusted odds ratio (AOR) of 1.04 (0.99-1.09) for small for gestational age.

Weak associations were also found between high residential exposure (PM_{10}) and low birthweight (<2500g), AOR 1.02 (0.97-1.08), compared to the very low exposed. The analysis of the continuous exposure variable AOR 1.02 (1.00-1.04) per $\mu g/m^3$ PM_{10} almost showed a significant increase of risk in relation to low birthweight. The difference between the 10th and

90th percentile of PM₁ exposure showed a statistically significant association with low birthweight, AOR 1.06 (1.01-1.10), and no increased risk was shown for preterm birth.

For PM₁₋₁₀, a similar pattern was found but with weaker associations and no clear associations was found between low birthweight or preterm birth and exposure to residential air pollution.

Table 5. Maternal residential exposure ^a to particles during pregnancy in relation to small for gestational age ^a, low birthweight ^b and preterm birth ^c.

	PM ₁ from local and urban sources				PM ₁₋₁₀ from local and urban sources			
	Crude n=546,049		Adjusted n=536,367		Crude n=546,049		Adjusted n=536,367	
	OR (95% CI)	No of cases	OR (95% CI)	No of cases	OR (95% CI)	No of cases	OR (95% CI)	No of cases
SGA								
per µg/m ³	1.04 (1.02-1.06)		1.02 (0.99-1.04)		1.02 (1.01-1.03)		1.00 (0.99-1.01)	
10 th to 90 th percentile	1.09 (1.04-1.14)		1.04 (0.99-1.09)		1.05 (1.02-1.09)		1.00 (0.96-1.04)	
Very low exposed	1	2,619	1	2,555	1	2,655	1	2,592
Low exposed	1.18 (1.12-1.24)	3,070	1.06 (1.01-1.12)	2,951	1.09 (1.03-1.15)	2,890	1.03 (0.97-1.08)	2,781
Moderate exposed	1.15 (1.09-1.22)	3,012	1.06 (1.00-1.12)	2,912	1.18 (1.12-1.25)	3,129	1.07 (1.01-1.13)	3,017
High exposed	1.17 (1.11-1.24)	3,061	1.07 (1.01-1.14)	2,980	1.17 (1.11-1.23)	3,088	1.04 (0.98-1.10)	3,008
LBW								
per µg/m ³	1.01 (0.99-1.02)		1.02 (1.00-1.04)		0.99 (0.98-1.00)		0.99 (0.98-1.00)	
10 th to 90 th percentile	1.02 (0.98-1.05)		1.06 (1.01-1.10)		0.98 (0.95-1.01)		0.98 (0.95-1.01)	
Very low exposed	1	3,925	1	3,848	1	3,885	1	3,803
Low exposed	1.01 (0.97-1.06)	3,980	0.98 (0.94-1.03)	3,869	1.02 (0.98-1.07)	3,975	1.01 (0.97-1.06)	3,883
Moderate exposed	1.00 (0.96-1.05)	3,943	1.01 (0.96-1.06)	3,842	1.03 (0.99-1.08)	4,015	1.02 (0.98-1.07)	3,904
High exposed	1.00 (0.96-1.05)	3,931	1.02 (0.97-1.08)	3,866	1.01 (0.96-1.05)	3,904	1.00 (0.95-1.05)	3,835
PTB								
per µg/m ³	0.97 (0.98-0.99)		1.01 (0.99-1.02)		0.98 (0.97-0.98)		0.99 (0.98-1.00)	
10 th to 90 th percentile	0.94 (0.91-0.97)		1.02 (0.98-1.05)		0.93 (0.91-0.95)		0.96 (0.93-0.99)	
Very low exposed	1	6,426	1	6,307	1	6,349	1	6,220
Low exposed	0.97 (0.94-1.01)	6,248	0.99 (0.95-1.03)	6,136	0.99 (0.96-1.03)	6,299	1.01 (0.98-1.05)	6,210
Moderate exposed	0.94 (0.91-0.97)	6,061	1.00 (0.96-1.04)	5,951	0.98 (0.94-1.01)	6,209	1.03 (0.99-1.07)	6,089
High exposed	0.91 (0.88-0.94)	5,879	0.98 (0.95-1.03)	5,799	0.90 (0.87-0.94)	5,757	0.95 (0.91-0.99)	5,674

- Small for gestational age, estimated by a calculated growth curve of weight and gestational age.*
- Low birth weight, dichotomised as <2,500 g and ≥2,500 g.*
- Preterm birth, dichotomised as <37 weeks and ≥37 weeks.*
- Exposure divided into unexposed; ≤0.01 µg/m³ (0-25th percentile), low exposure; 0.01 µg/m³>, ≤0.72 µg/m³ (>25-50th percentile), moderate exposure; 0.72 µg/m³>, ≤1.57 µg/m³ (>50th-75th percentile, and high exposure; 1.57 µg/m³> (>75th percentile) for PM₁ and unexposed; ≤0.05 µg/m³ (0-25th percentile), low exposure; 0.05 µg/m³>, ≤0.48 µg/m³ (>25-50th percentile), moderate exposure; 0.48 µg/m³>, ≤1.50 µg/m³ (>50th-75th percentile, and high exposure; 1.50 µg/m³> (>75th percentile) for PM₁₋₁₀.*
- Restricted on smoking and occupation in text (not missing), tunnels and single births.*
- Adjusted for mother's age, smoking habits, occupational exposure, education, socioeconomics, exposure to ground level ozone, nationality, parity and birth year of the child*

4.3 Combined occupational and residential exposure

The results of the joint analysis between residential exposure (PM₁) and occupational exposure is shown in Table 6.

The results showed lower birthweight with higher occupational exposure and the same with higher residential exposure. In the joint analysis between residential exposure (PM₁) and occupational exposure, no interaction effect was seen, but when comparing the results with the moderate exposure to residential exposure and low occupational exposure an additive effect was suggested. There was a weaker association in the groups with high residential exposure and moderate to high occupational exposure compared with the medium residential exposure with the same occupational exposure levels. The patterns were similar between residential exposure to PM₁ and PM₁₋₁₀.

Table 6. Interaction analyses between occupational and residential exposure (PM ₁) to air pollution in relation to <u>birthweight in grams</u>						n=111,867
Residential exposure PM ₁ ^a						
Occupational exposure	Low <33 th percentile	n	Medium 33 th to 66 th percentile	n	High >66 th percentile	n
Unexposed	0.0	38,092	- 6.2(- 14.7, 2.3)	34,616	- 13.1(-22.3,-3.9)	34,885
Low < 50 th percentile	- 17.8(-61.0, 25.4)	667	- 66.2(-115.3,-17.2)	514	- 29.8(-82.2,-22.5)	453
High >50 th percentile	- 59.0(-90.1,-29.0)	1,309	- 64.2(-104.8,-23.6)	756	- 60.0(-106.5,-13.4)	575
^a = Residential exposure for PM ₁ from local and urban sources divided into low <0.14 µg/m ³ , medium 0.14 – 1.24 µg/m ³ and high > 1.24 µg/m ³ . ^b = Occupational exposure divided on the median for the exposed 0.04 mg/m ³ into unexposed, low exposure and high exposure ^c = Restricted on smoking, occupation (not missing), working at all, low absence from work, tunnels and single births and education lower than University ≥3 years or Graduate. ^d = Adjusted for mother's age, smoking habits, education, socioeconomics, exposure to ground level ozone, nationality, parity and birth year of the child.						

5 DISCUSSION

The results showed that high exposure to inorganic or organic particles among full-time working mothers with less than 50 days (median) leave of absence during pregnancy was associated with low birthweight and pre-term births, as well as small for gestational age compared to unexposed.

Subanalysis on inorganic exposures revealed that the association was mainly driven by iron particles, including welding. Subanalysis of organic particles showed that the results were mainly driven by cooking fumes, oil mist, other organic dust, and paper dust. However, we suspect that all these exposures co-exists with combustion related particles, and we cannot rule out that combustion related exposure might have influenced the results. These findings are supported by previous studies on combustion derived products (such as PAH) and are strengthened by mechanistic data on PAH and the disruption of normal placental function (Langlois et al., 2014, Møller et al., 2014, Miller et al., 2015, Miller et al., 2004, Barr et al., 2007).

The exposure to concrete (and stone), wood, animal, textile, flour, other inorganic particles and diesel exhaust was not associated to adverse birth outcomes in this study. With the exception of diesel exhaust, the other particles are mainly coarse particles, depositing in the nasopharyngeal region. We did not find any previous study on exposure to concrete and adverse birth outcomes (Lipfert, 2018), but coarse organic particles, with a focus on the textile industry, showed results in line with our findings, with no increased risk for adverse birth effects among pregnant mothers (Savitz et al., 1989, Savitz et al., 1996).

When it comes to diesel exhaust (NO_2), the lack of increased risk was unexpected at first, but checking previous research, it seems that the levels of diesel engine exhaust in the exposed group in our study might be too low to show any adverse birth effects (Lewné et al., 2007).

Combustion related particles (PM_{10}) in the residential area during pregnancy showed weak associations between high exposure (PM_{10}) and small for gestational age, AOR 95%CI 1.07 (1.01, 1.14), and low birthweight ($<2500\text{g}$), AOR 1.02 (0.97-1.08), but no increased risk of preterm birth was shown. NO_2 and NO_x have also been used as a marker for traffic pollution and the result of PM_{10} and small for gestational age is in line with previous Swedish studies that showed weak associations between NO_x and small for gestational age (Olsson et al., 2015, Malmqvist et al., 2011).

However, when analysing the reduction in birthweight a statistically significant association was seen, comparing High exposed -29.0g (95%CI: -33.6g;-24.5g), Moderate exposed -24.1g (95%CI: -28.4g;-19.8g) and Low exposed -15.3 g (95%CI: -19.4 g; -11.1 g) to Very low exposed. This pattern was also seen for PM_{10-10} regarding birthweight, but not small for gestational age, low birthweight or preterm birth. A similar pattern was seen in a systematic review regarding NO_2 associated with birthweight and low birthweight (Stieb et al., 2012).

Figure 8 showed that the reduction in birthweight in our study seemed to affect normal weight to heavier children to a larger extent than children with low birth weight. This could be the reason for the lack of association between the outcome measures low birth weight (<2500g) and small for gestational age in relation to residential air pollution. This association have been seen previously in a study on ambient air pollution in association with birthweight (Strickland et al., 2019).

Being born small for gestational age and low birthweight are dichotomised values and the effect of residential air pollution on birth outcomes mainly showed a general decrease in birthweight for normal to heavier children, therefore these outcomes measures are not suitable for capturing the effect of adverse birth outcomes produced by residential exposure to air pollution. What effects a decreased birthweight in heavier children is less known (Oken, 2013).

When looking at the reduction in birthweight and comparing High exposed -29.0g (95%CI: -33.6g;-24.5g), Moderate exposed -24.1g (95%CI: -28.4g;-19.8g) and Low exposed -15.3 g (95%CI: -19.4 g; -11.1 g) to Very low exposed in our study, the results could be compared to a study on maternal smoking and its association with birthweight (Bernstein et al., 2005) where they estimated a 27g reduction in birthweight for each additional cigarette per day that the pregnant women smoked in the third trimester. This is similar to the reduction our results showed for the high exposed.

Interaction analyses between occupational and residential exposure to air pollution was also made.

The results show no clear interaction effect, but an additive effect was shown, indicating that joint exposure can increase the risk of adverse birth effects. No previous study was found on interaction analyses on occupational and residential exposure in association with pregnancy outcome and further studies are there for needed to confirm this finding. Occupational exposure was also used as a confounder in the analyses on residential exposure to particles, but the confounding effect was marginal. Residential studies on air pollution in Sweden (especially on a national level) are therefore not likely confounded by occupational exposures to particles.

While mothers' exposure to residential ambient air pollution during pregnancy and adverse birth outcomes has been intensely investigated, occupational exposure to pollutants has not been as studied, even though levels can be at substantially higher in occupational setting compare to residential. In our study, we had access to the residential air pollution exposure levels in combination with estimations on occupational exposure to particles during pregnancy and this gave us a unique opportunity to assess the relationship between these two exposures and adverse births effects.

In all of the included articles in this thesis, a major strength is the large amount of observations, both for the occupational and the residential setting. Another great strength is

the detailed information on possible confounders, outcomes and exposure assessments (both for occupational and residential exposure). The information regarding employment status that was collected at the interview in the beginning of the pregnancy and the exposure assessments that were performed objectively and blinded to the outcome have minimized the problem with recall bias in this study. Recall bias is otherwise a common systematic error in reproductive studies. The study had good coverage (with about 99% of all births included in the Medical Birth Register, (Cnattingius et al., 2016) with few missing values. The model for ambient air pollution estimates (SIMAIR) is extensive and has been validated (Andersson and Omstedt, 2013).

When making models they always simplify the reality and there are of course weaknesses, but as long as the weaknesses are managed and of subordinate meaning, models are often cost effective and sometimes the only possible way to conduct large studies (Kauppinen et al., 2014). The different weaknesses mainly concerned the information on possible confounders and exposure assessments (both for the residential and occupational setting). The occupational exposures were assessed with job exposure matrices. A job exposure matrix works as a tool for assessing occupational exposure at a group level in large epidemiological studies, but it is not equal to individual measurements. The measurements done for different occupations were calculated in to concentration and prevalence, and these were then used as mean levels for different occupational groups. The job exposure matrix might therefore introduce a misclassification. The misclassification would probably be non-differential, and as such mainly push the risk down in the middle and high exposed groups, leading to an underestimation of the risk.

Another weakness connected to epidemiological occupational studies is residual confounding related to socioeconomic factors which may be more connected to the occupation rather than to the exposure. Similar weakness can be seen in epidemiological studies with residential air pollution exposure where the socioeconomics (e.g. income) could be more related to geographical location rather than to the exposure. Income is also problematic as a socioeconomic confounder for other reasons, such as low income during pregnancies (because of absence or other reasons) which might not be a reflection of the mother's socioeconomic status. Other confounders may also be affected, such as parity and age, which may be more related to location rather than exposure, all leading to an underestimation of the risks.

We used information on absence from work to assess the exposure more precisely in the occupational settings and reduce the misclassification of exposure. The absence from work was also used to manage the risks of residual confounding in form of socioeconomic effects that could be related to occupation rather than exposure, when using a job exposure matrix. Residual socioeconomic confounding seems unlikely since effects was mainly seen in mothers with low absence from work, but not in mothers with the same occupation and high absence from work.

However, the use of information on absence still had some limitations. First, the information on absence does not include short-term sick leave, which might lead to underestimating the risk because of non-differential misclassification. The other limitation was the relocation or change of work task during pregnancy which we did not have any information about, but which we suspect might have led to underestimations. Also, we did not have any information about miscarriages, which if they were caused by exposure, would lead to an attenuation of the results.

There were also some potential confounders that we did not have in the model, such as noise, which has been associated to adverse pregnancy outcome (Selander et al., 2016) and is correlated to traffic related exposure. This could be a question for future research, but it was also shown in the occupational studies where we adjusted for occupational noise, that particles had an independent effect on the outcome. If they are too correlated there is then a risk of over adjustment which would then again lead to an underestimation of the true risk of particle exposure.

High correlation with traffic derived particles from local and urban sources is also the reason why we choose to not adjust for NO₂. Exposure to NO₂ can by itself lead to respiratory irritation and is highly correlated to PM₁. It is a bit similar to smoking, where there are a lot of possible harmful agents in the smoke that cause adverse health effects. Therefore, it is not possible today to claim which agent/s in ambient air from local and urban sources cause the adverse outcomes (Li et al., 2017). There is a study on mortality associated to short-term exposure of air pollution, which discusses behavioral factors as a cause for misclassification and a reason for why an increased risk of mortality was shown in association with PM_{2.5-10}, but not when analysing small particles and NO₂ (Henrik et al., 2019).

This mixture of exposures from traffic-related emissions is not easily disentangled and was something we could see in our study too, especially when using birthweight (in grams). The pattern of increased risks was similar between PM₁ and PM₁₋₁₀ which is probably an effect of the high correlation between small and large particles as well as NO₂. Some evidence of combustion related agents affecting the placenta has emerged in recent years on a mechanistic level, for example PAH has been shown to transfer (Miller et al., 2004, Barr et al., 2007) and soot particles which have also been discovered (Bové et al., 2019).

The exposure to regional background shows less variability in comparison to local and urban sources, with its slight gradient between east and west and south and north. It is, on the other hand, not that correlated to local and urban sources of emissions and that is also why we did not adjust for regional background and geographical information on a regional scale. Another limitation of the residential air pollution estimates is that they do not account for the canyon effect (Amorim et al., 2013), which can lead to under or overestimations of the exposure on any given address. This would also lead to a non-differential misclassification.

Today there are no Swedish regulations of PM_1 regarding ambient air pollution; the closest are $PM_{2.5}$ and possibly NO_2 . On the other hand, PM_{1-10} from local and urban sources showed a similar pattern, possibly due to similar source and high correlation, and if the relationship between compounds stays the same, regulations targeting NO_2 for instance, would also have an effect on the amount of small and larger particles from that same source.

However, the presumably more potent particles from local and urban sources would probably not be the dominant factor for PM_{10} and $PM_{2.5}$ and to regulate those further would probably mainly target the levels in regional backgrounds. The regional background could also be much harder to affect within Sweden, where they are largely composed of European emissions and sea salt, among others. Sweden's levels of ambient air pollution are generally very low compared to other countries in Europe (Pedersen et al., 2013), but we could still see an effect in our study. The first action might be to further investigate the relationship between PM_1 , PM_{1-10} and NO_2 from local and urban sources and perhaps to also take further measurements of the PM_1 content found in the ambient air pollution at the regional backgrounds.

Among the exposed working mothers, the median value of organic particles was 0.08 mg/m^3 and 0.09 mg/m^3 for both inorganic and welding fumes. Both could be compared to stipulated levels of organic dust; inhalable (PM_5) of 5 mg/m^3 , and inorganic dust; inhalable (PM_5) of 5 mg/m^3 , and respirable ($PM_{3.5}$) of 2.5 mg/m^3 , from 'Hygieniska gränsvärden (AFS 2018:1)'. The levels in these studies are generally lower than the regulated amounts.

6 CONCLUSION AND FUTURE RESEARCH

Separate effects on birthweight were seen after exposure to particles in occupational and/or residential setting. Occupational exposure to organic (e.g. oil mist, paper dust, cooking fumes and other organic particles) and inorganic particles (e.g. iron particles), as well as combustion products (PAH) and welding fumes, have shown to be associated with an increased risk of adverse birth outcomes. The results strengthen the view that women should not be exposed to high levels of these particles during pregnancy, but the results needs to be confirmed in future studies.

Residential exposure to particles was associated with decreased birthweight. Only marginal effects were seen when adjusting for occupational exposure in the analyses of residential exposure and birth outcomes. This suggests that there are no need for adjustment for occupational exposure in studies of residential exposures and birth effects. An additive effect of both residential and occupational exposure to particles was suggested. These results imply that for individual risk assessments an overall exposure assessment of particles is needed. These results need also to be confirmed in future studies.

In future research it would be of great interest to study a larger population and to have the power to investigate the suggested additive effects of occupational and residential exposure further. To study populations were they are exposed to fractions of particles that are less correlated than in Sweden would be of interest. It would also be of interest to adjust for further confounding, such as noise, regarding the residential air pollution in the model. The JEM could be developed further and validated. Some confounders, such as parity, could be further investigated to be able to distinguish mechanistic effects from potential mediating effects.

Regarding possible additive effects, the commuting could be included in the overall exposure measurements in order to assess individual risks more precisely. The mechanistic effect of exposure and outcome should also be investigated further. This will be of great importance on an individual level as well as on a population level, giving data for urban planning along with risk assessments and recommendations during pregnancy.

7 POPULÄRVETENSKAPLIG SAMMANFATTNING

Luftföroreningar är en av de största miljöfaktorerna som påverkar hälsan negativt och leder till för tidig död i ett globalt perspektiv. Luftföroreningar har blivit associerade med flera negativa hälsoutfall, däribland hjärt- och kärlsjukdomar, cancer och luftvägssjukdomar. Luftföroreningar har också associerats med negativa graviditetsutfall i form av låg födelsevikt, liten för tiden och för tidig födsel. Det har gjorts en del studier på luftföroreningar i utomhusmiljön och graviditetsutfall, men det är fortfarande oklart vilka partiklar i luftföroreningarna som ligger bakom associationen.

I arbetsmiljön har det gjort betydligt färre studier av luftföroreningar i partikelform och graviditetsutfall. Dock är det många kvinnor som utsätts för olika former av luftföroreningar i arbetsmiljön och halterna kan vara betydligt högre än i utomhusmiljön. Något som knappt ej heller har studerats är samverkande effekter mellan luftföroreningar i arbets- och utomhusmiljö.

Vårt övergripande mål i denna avhandling har varit att undersöka associationen mellan moderns exponering under graviditeten i arbets- och utomhusmiljö i förhållande till graviditetsutfall.

För att göra det byggde vi en databas med uppgifter ifrån olika svenska register som kopplades till information om graviditeter, hämtade från Medicinska födelseregistret från 1994 till och med 2012. Medicinska födelseregistret innehåller en lång rad uppgifter om graviditetsutfall och uppgifter som behövs för att justera analyserna, såsom rökvanor, moderns ålder och paritet mm. Det var totalt ungefär två miljoner graviditeter.

För att uppskatta exponeringen av olika partiklar i arbetsmiljön användes en yrkesexponeringsmatris som kopplades till moderns uppgifter om yrke. En yrkesexponeringsmatris är en tabell med uppskattningar av nivåer och förekomst av föroreningar i olika yrkesgrupper. I den här studien var exponeringen partiklar i luften som vi huvudsakligen grupperade i organiska- och organiska partiklar, men vi studerade även särskilt på svetsrök och förbränningsrelaterade partiklar som PAH och dieselavgaser (i form av kvävedioxid). Förbränningsrelaterade partiklar är ofta mycket mindre än de andra partiklarna, vilket gör att de kan ta sig längre ner i lungorna. Vi analyserade även subgrupper av de organiska- och organiska partiklarna för att se vilka ämnen som gav resultaten. Likaså la vi till uppskattningar om andra yrkesexponeringar såsom yrkesbuller, som vi använde att justera resultatet med i analyserna. En viktig uppgift för att kunna bedöma exponeringen var frånvaro från arbetet, tack vare uppgifter från försäkringskassan kunde vi dela upp mödrarna i grupper med låg, mellan och hög frånvaro.

Studien tittade vidare på ett urval av graviditeterna för att analysera utomhusmiljöexponeringen av luftföroreningar och samverkan med yrkesexponeringen i relation till negativa graviditetsutfall. Urvalet utgjordes av ca 500 000 adresser, från 2007 till

och med 2012, som mödrarna hade bott på under graviditeten. Dessa adresser använde vi sedan för att uppskatta luftföroreningsnivån i utomhusluften genom ett modelleringsverktyg som kallas SIMAIR. Luftföroreningarna delades upp i stora (PM_{1-10}) och små partiklar (PM_1).

Resultaten visade att organiska partiklar (oljedimma, stekos, pappersdamm, och övriga organiska partiklar) och delvis oorganiska partiklar (järndamm) tillsammans med förbränningsrelaterade partiklar (PAH) och svetsrök var associerade med en högre risk för negativa graviditetsutfall.

När det gäller utomhusexponering var resultaten lite mer blandade, både stora och små partiklar var associerade med lägre födelsevikt i gram, ungefär motsvarande effekten av att modern skulle röka en cigarett om dagen under graviditeten. Tecken på en additiv effekt sågs också mellan luftföroreningar utomhus och i yrket i relation till födelseutfall. Vi hittade endaste marginella skillnader i resultat när vi justerade för yrkesexponeringen i utomhusexponeringsanalyserna. Vi anser dock att det är viktigt att se till alla luftföroreningskällor vid riskbedömning av luftföroreningar under graviditeten.

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